

Experimental Cinchophen Ulcer.*

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The cinchophen ulcer has been studied extensively since the first observations of Churchill and Van Wagoner.¹ Stalker, Bollman and Mann have examined the problem of the cinchophen ulcer most thoroughly, and have reported their findings in several recent publications.^{2, 3, 4} Our laboratory has been interested in this problem for evaluation of ulcer therapy, and herein are presented our observations, some of which are at variance with previous findings.

Chronic Feeding Experiments. Seven dogs weighing from 8 to 14 kg were fed a diet of kitchen scraps (without bones), white bread, yeast, bone meal, salt, and cod liver oil to which was added daily 1 to 5 g of cinchophen.†

Results. A 9.5 kg female white Spitz died after receiving 1 g of cinchophen daily for 12 days. Necropsy revealed a large perforated ulcer surrounded by smaller ulcerations on the proximal posterior aspect of the pyloric canal. A second white Spitz received 3 g of cinchophen daily for 10 days. The animal's weight declined from 8 to 6 kg, and it was found dead on the morning of the 11th day. Autopsy showed empyema of the chest and numerous small ulcerations of stomach and duodenum. One large shallow ulcer 3 cm in diameter was situated at the entrance of the pylorus. A third white Spitz (11 kg) received 25 g of cinchophen during a period of 20 days. The animal lost weight, refused to eat and became cachectic, but stools did not become tarry. Sixteen days after stopping the administration of cinchophen the animal died. At necropsy a number of acute small ulcers were found in the antral region of the stomach and in the first portion of the duodenum. A large,

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¹ Churchill, T. P., and Van Wagoner, F. H., *Proc. Soc. Exp. Biol. and Med.*, 1931, **28**, 581.

² Stalker, L. K., Bollman, J. L., and Mann, F. C., *Arch. Surg.*, 1937, **35**, 290, 294.

³ Bollman, J. L., Stalker, L. K., and Mann, F. C., *Arch. Int. Med.*, 1938, **61**, 119.

⁴ Stalker, L. K., Bollman, J. L., and Mann, F. C., *Arch. Surg.*, 1937, **34**, 1172, 1174, 1176.

† We are obliged to Dr. D. A. Bryce of the Calco Chemical Company for supplying the cinchophen.

deep chronic ulcer 2 x 2 cm in diameter was found near the pylorus on the posterior wall of the stomach.

The following 4 animals were of mixed breed. The fourth animal (9 kg) was fed a total of 14 g of cinchophen over a period of 14 days; no tarry stools, anorexia or loss of weight appeared. One month later 138 g of cinchophen were fed over a period of 48 days, at the end of which laparotomy with opening of stomach and duodenum failed to disclose peptic ulcerations. The stools were persistently negative for blood. The fifth dog (13.5 kg) was fed 4 g of cinchophen in 4 days. He then had complete anorexia but no tarry stools. We suspected a perforating, non-bleeding ulcer and laparotomy was performed. Stomach and duodenum were opened, but no ulceration, gastritis or duodenitis observed. A few days later the animal died of pneumonia which probably had begun earlier and had caused anorexia. Autopsy did not reveal gastrointestinal pathology. In dogs dying from pneumonia or distemper, gastritis and erosions are not infrequent. The sixth and seventh dog (12 and 14 kg) received 19 and 74 g of cinchophen in 19 and 24 days respectively. No tarry stools or other symptoms of ulcer were noted in either of these dogs.

It has been shown that the development of ulcer from oral administration of cinchophen is variable from the point of view of onset. Practically every experimenter in this field has found a small percentage of animals in which no ulcers developed under administration of cinchophen or certain other drugs even in high doses. In a comparable series of experiments by Stalker, Bollman and Mann ulcer developed in 11 out of 12 dogs that were not fed bone, in an average of 18 days after the administration of 36 g of cinchophen.² In our series 3 dogs died and peptic ulcers were found at necropsy; the remaining 4 did not show evidence of ulceration during periods of administration of the drug of 4, 19, 24, and 47 days, although daily doses of approximately 3 and 4 g were given to the last 2 dogs. On the other hand the 3 dogs that died had been fed smaller doses of the drug over shorter periods of time (1, 2 and 3 g per day over 12, 20 and 10 days respectively). It is, therefore, of interest to point out that these 3 animals were white Spitzes. Perhaps this species of dog is more susceptible to cinchophen ulcers than others. A second point is that one of these animals died 16 days after the last dose of cinchophen and stomach and duodenum contained a number of acute ulcers, as well as one large chronic prepyloric ulceration. Stalker, Bollman and Mann² found that no new ulcers are formed and that chronic ones begin to heal practically immediately

after cessation of administration of the drug. Hence, in the above dog, the etiologic cause for the acute and chronic ulcers remains open.

Effect of Cinchophen on Pouch Secretion. Four dogs with Heidenhain pouches, drained by a metal cannula were used. Their body weights were from 15 to 25 kg, with an average of 22 kg. Twice a week secretion of the pouch was stimulated by subcutaneous injection of 1 mg of histamine acid phosphate every half-hour for a period of 3 hours. This method was chosen in order to establish the maximum secretory capacity of the oxyntic cells. Free and total acidity were titrated against dimethyl-amino-azobenzene and phenolphthalein. Control studies of gastric secretion were performed for several weeks, and cinchophen was administered intravenously as the neutral sodium salt, so as to be certain that the full dose was given and retained. The dose was 1 to 2 g per injection, given 4 to 6 times a week. Total amounts of drug administered to the 4 dogs were as follows: 32 g in 16 days, 32 g in 39 days, 12 g in 15 days, 50 g in 25 days, and one month later 28 g in 22 days. Several of the animals did not bleed from their pouch until 12 or more injections of cinchophen had been given; at that time they showed symptoms of early gastritis, such as occasional tarry stools, vomiting and bleeding from the pouch, but analyses of histamine-stimulated secretion showed no increase in volume secretion at any time during the period of administration of the drug. As a matter of fact the amount of secretion decreased somewhat and became irregular. Free and total acidity also tended to diminish and fluctuate erratically, independent of occasional bleeding from the pouch. In one dog the highest values for free and total acidity were observed when bleeding began, just one day before death. Autopsy revealed peritonitis from perforated duodenal ulcer, just beyond the pyloric ring. Gastritis was present in main stomach and pouch; this was the only animal in the series which died or perforated.

Stalker, Bollman and Mann⁴ found an increased volume secretion in their pouch dogs following administration of cinchophen when symptoms of early gastritis, such as tarry stools and occasional vomiting appeared. When administration of cinchophen was discontinued, a gradual decrease in the amount of gastric secretion to the normal level occurred within 2 weeks. They employed food as secretagogue for their pouch dogs and histamine for their dogs with intact stomachs. Gastric juice was collected continuously from their pouch dogs, but secretion tests on their dogs with intact stomachs was done every second or third day. The dogs of the latter group

(17 kg average weight) received one dose of 1.5 mg of histamine subcutaneously. Yet the results obtained in both groups of animals were identical with regard to increased volume of secretion. The administration of 0.5 g or more of cinchophen caused evidence of gastritis in every dog within 8 hours after the initial dose; when the dose was 1 g or more daily, ulcers developed in from 2-5 days and usually perforated.⁴

The discrepancy between our results and those of Stalker, Bollman and Mann can hardly be found in the fact that our technical procedures were different. Our pouch dogs (22 kg average weight) received 1 mg of histamine every half hour for 3 hours (total of 6 mg). We feel that an augmented volume of secretion would certainly have been found by this method. Our pouch dogs received roughly similar individual doses of cinchophen by vein and for longer periods than did the pouch dogs of Stalker, Bollman and Mann⁴ by mouth, *i. e.*, larger total amounts of the drug, and yet only one animal died from perforated gastric ulcer while the rest survived. It has been shown that the drug acts after absorption, and not locally,⁵ or after excretion into the stomach from the blood.² Therefore one cannot assume that oral or intravenous administration of cinchophen should have different effects. Furthermore, vomiting may cause loss of orally administered drug. It may be that our preparation of cinchophen varies in some way from that of the above and other workers.[‡]

Summary and Conclusions. 1. White Spitz dogs seem more prone to develop cinchophen ulcers than other species of dogs. 2. Heidenhain pouch dogs receiving cinchophen intravenously show no increase in volume secretion under histamine stimulation.

⁵ Churchill, T. P., and Manshardt, D. O., *PROC. SOC. EXP. BIOL. AND MED.*, 1933, **30**, 825.

[‡] Cinchophen Calco, Lot No. 24331 and 29056 were used.